unresponsiveness and loss of TGF-beta receptor type II expression caused by histone deacetylation in lung cancer cell lines.

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SOURCE: CANCER RESEARCH, (2001 Nov 15) 61 (22) 8331-9. Journal code: 2984705R. ISSN: 0008-5472.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200112

ENTRY DATE: Entered STN: 20011126
Last Updated on STN: 20020123
Entered Medline: 20011212

AB Transforming growth factor (TGF)-beta strongly inhibits epithelial cell proliferation. Alterations of TGF-beta signaling are thought to play a role in tumorigenesis. We show in the present study that most lung ***cancer*** cell lines have lost the growth-inhibitory response to TGF-beta signal, and that those with TGF-beta unresponsiveness can be divided into two major groups, TGF-beta type II receptor (TGFbetaRII)(+)/Smad7(+) and TGFbetaRII(-)/Smad7(-), suggesting the heterogeneous mechanisms underlying the TGF-beta responsiveness. The mechanism of the loss of TGFbetaRII expression of the latter group was further studied, identifying aberrant ***DNA*** ***methylation*** of the promoter region in a limited fraction of cell lines. Interestingly, we found that the alteration of chromatin structure because of histone deacetylation may also be involved, showing a good correlation with loss of TGFbetaRII expression. This notion was supported by the findings of a restriction enzyme accessibility assay, of a chromatin immunoprecipitation assay with anti-acetyl histone antibodies, and of an in vivo induction of TGFbetaRII expression by ***histone*** ***deacetylase*** ***inhibitors*** including ***trichostatin*** ***A*** (TSA) and sodium ***butyrate*** . In vitro induction of TGFbetaRII promoter reporter activity by TSA was also detected and found to require the CCAAT box within the -127/-75 region. A positive regulatory mechanism for TGFbetaRII expression in a TGF-beta-expressing cell line was also investigated, and a TPA-responsive element (TRE)-like motif, TRE2, was detected in addition to the previously reported TRE-like motif Y element in the positive regulatory region. Alterations in two discrete proteins interacting with these two TRE-like motifs were also suspected of being involved in the loss of TGFbetaRII expression. This is the first study to demonstrate that, in addition to the TSA-responsive region and TRE2 motif in the TGFbetaRII promoter, the alteration of histone deacetylation may be involved in the loss of TGFbetaRII expression in lung ***cancer*** cell lines.

L15 ANSWER 5 OF 23 MEDLINE

ACCESSION NUMBER: 2001184179 MEDLINE

DOCUMENT NUMBER: 21139057 PubMed ID: 11245429

TITLE: DNA methyltransferase inhibition enhances apoptosis induced by histone deacetylase inhibitors.

AUTHOR: Zhu W G; Lakshmanan R R; Beal M D; Otterson G A

CORPORATE SOURCE: Department of Internal Medicine and the Comprehensive Cancer Center, The Ohio State University, Columbus 43210-1240, USA.

CONTRACT NUMBER: 1 R25 CA82351 (NCI)
P30 CA16058 (NCI)

SOURCE: CANCER RESEARCH, (2001 Feb 15) 61 (4) 1327-33. Journal code: 2984705R. ISSN: 0008-5472.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200103

ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329

AB Histone acetylation has long been associated with transcriptional

study of orally formulated and administered SAHA demonstrates oral bioavailability and evidence of efficacy without apparent toxicity.

L15 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:743205 CAPLUS
DOCUMENT NUMBER: 136:35591
TITLE: Synergistic activation of functional estrogen receptor (ER)-.alpha. by DNA methyltransferase and histone deacetylase inhibition in human ER-.alpha.-negative breast cancer cells
AUTHOR(S): Yang, Xiaowei; Phillips, Dawn L.; Ferguson, Anne T.; Nelson, William G.; Herman, James G.; Davidson, Nancy E.
CORPORATE SOURCE: The Johns Hopkins Oncology Center, Johns Hopkins University, Baltimore, MD, 21231, USA
SOURCE: Cancer Research (2001), 61(19), 7025-7029
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Formation of transcriptional repression complexes such as DNA methyltransferase (DNMT) 1/histone deacetylase (HDAC) or methyl-CpG binding protein/HDAC is emerging as an important mechanism in silencing a variety of methylated tissue-specific and imprinted genes. Our previous studies showed that treatment of estrogen receptor (ER)-.alpha.-neg. human breast cancer cells with the DNMT inhibitor 5-aza-2'-deoxycytidine (5-aza-dC) led to ER mRNA and protein re-expression. Also, the HDAC inhibitor trichostatin A (TSA) could induce ER transcript about 5-fold. Here we show that 5-aza-dC alone induced ER transcript about 30-40-fold, and the addn. of TSA elevated ER mRNA expression about 10-fold more in the human ER-neg. breast cancer cell lines MDA-MB-231 and MDA-MB-435. Overall, the combination of 5-aza-dC and TSA induced a 300-400-fold increase in ER transcript. Restoration of estrogen responsiveness was demonstrated by the ability of the induced ER protein to elicit estrogen response element-regulated reporter activity from an exogenous plasmid as well as induce expression of the ER target gene, progesterone receptor. The synergistic activation of ER occurs concomitantly with markedly reduced sol. DNMT1 expression and activity, partial demethylation of the ER CpG island, and increased acetylation of histones H3 and H4. These data suggest that the activities of both DNMT1 and HDAC are key regulators of methylation-mediated ER gene silencing.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 14 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:419730 BIOSIS
DOCUMENT NUMBER: PREV200200419730
TITLE: Enhancement of antineoplastic action of 5-aza-2'-deoxycytidine (***Decitabine***) by ***histone*** ***deacetylase*** ***inhibitors*** against ***tumors*** and ***leukemia*** .
AUTHOR(S): Primeau, Melanie (1); Gagnon, Jacynthe; Shaker, Sepideh; Boivin, Anne-Julie; Hurtubise, Annie; Lemaire, Maryse; Momparler, Louise F.; Momparler, Richard L.
CORPORATE SOURCE: (1) Dept. Pharmacologie, Centre de Recherche Hopital Ste-Justine, Universite de Montreal, Montreal, QC Canada
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 1117. print.
Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L15 ANSWER 15 OF 23 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:261637 BIOSIS
DOCUMENT NUMBER: PREV200000261637
TITLE: Chemotherapy of breast ***cancer*** with ***inhibitors*** of ***DNA*** ***methylation*** 5-aza-2-deoxycytidine and histone deacetylation ***trichostatin*** ***A*** .